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OUTCOMES

Risk Factors for Acute Rejection in 806 Cyclosporine-Treated Renal Transplants: A Multivariate Analysis

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IT is known that acute rejection (AR) is responsible for serious graft injury, causing parenchymal deterioration that can end in early graft failure[1] or in long-term development of chronic dysfunction.[2] Both mechanisms contribute negatively to graft survival.[3,4] The aim of this study was to investigate the incidence, the causes, and the effects of AR on the outcome of transplants under cyclosporine (CyA)-based therapy.

PATIENTS AND METHODS

We analyzed 866 renal transplants performed between December 1985 and December 1999: of these, 854 (98.6%) were from cadaveric (834 primary transplants and 20 retransplants) and 12 (1.4%) were from living related donors. Acute rejection was biopsy-proven in 35%; in 65% it was diagnosed by clinical and laboratory elements, among which the most relevant was a serum creatinine (SCr) increase of at least 0.4 mg/dL. Sixty transplants were not included, either because the diagnosis of AR was not available or because nonimmunologic causes, such as vascular thrombosis or death, were responsible for the early graft loss. Therefore, 806 renal transplants (794 from cadaveric and 12 from living donor) remained eligible for the study. Steroid-based therapy was the AR treatment of choice. Antibody therapy was used for steroid-resistant AR. A diagnosis of chronic dysfunction (CD) was based on a progressive decline of renal function with a SCr $\geq$2.5 mg/dL.

We investigated the following parameters: namely in the donor (age, cause of death, perfusion solution, cold ischemia time [CIT], and SCr before retrieval), in the recipient (age, weight, associated pathology, HLA mismatches, and immunosuppression), and in the transplant course (delayed graft function [DGF], SCr at the end of the first year, and CD). Evaluation of transplant variables included the influence of DGF on AR incidence and, in contrast, the influence of AR on the SCr in the first year and on CD occurrence. We did not consider sensitization because the panel reactive antibody (PRA) rate proved to be irrelevant (2%). The cytomegalovirus status was not available. From database constructed with the records of all donors and recipients, a multivariate analysis was performed using logistic regression and univariate techniques with the Fisher Exact Test. We used the Kaplan-Meier method to calculate survival and the log-rank test to compare survival rates between the two groups (with AR or without AR). For all tests a P value $<.05$ was considered significant (two-tailed).

RESULTS

Acute rejection was diagnosed in 300 (37%) of the 806 renal transplants. A multivariate analysis showed that the risk factors for AR were cerebrovascular stroke as a cause of death in the cadaver donor (54% vs 35%), graft perfusion with Euro-Collins solution (42% vs 33%), cold ischemia time (CIT) >24 hours (44% vs 34%), and recipient age <45 years (42% vs 30%) (Table 1). The difference in the incidence of AR between the groups with 6, 5, 4 versus 3, 2, 1 HLA mismatches was not significant (39% vs 35%). The quadruple immunosuppressive regimen of antilymphocyte globulin (ALG) + azathioprine (Aza) + prednisone (Pred) + CyA was associated with the highest (46%) incidence of AR, and micophenolate mofetil (MMF) + CyA + Pred, the lowest (30%) risk. Acute rejection was more frequent among patients with DGF (48% vs 35%), and AR was responsible for 4.7% of graft losses (11 grafts of 236).

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Table 1. Risk Factors for Acute Rejection

Factors	*P* Value	Odds Ratio	CI 95%
Donor age	NS		
Donor cause of death (CVS)	.018	1.813	1.108–2.966
Perfusion with Euro-Collins solution	.007	1.508	1.118–2.033
CIT	.039	1.398	1.017–1.922
Recipient age <45 years	.000	1.871	1.366–2.562
Recipient weight	NS		
Recipient-associated pathology	NS		
HLA mismatches	NS		
ALG + Aza + Pred + CyA	.004	2.017	1.248–3.258
DGF	.008	1.714	1.162–2.527

Abbreviations: CVS, cerebrovascular stroke; CIT, cold ischemia time; ALG, antilymphocyte globulin; Aza, azathioprine; Pred, prednisone; CyA, cyclosporine; DGF, delayed graft function.

Regarding the influence of AR on transplant evolution (Table 2), we observed significantly worse renal function at 1 year evaluated as a SCr >1.2 mg/dL, namely 46% vs 27%, and a higher CD incidence, namely 40% vs 12%. This higher CD incidence is particularly important because CD emerged as the second cause of graft failure, with a rate of 30.5%, after death with a functioning graft (DWFG), namely 41.5%.

Graft survival rates at 1, 3, 5, 10, and 15 years were 94%, 85%, 74%, 49%, and 37% in the AR group, respectively, and 97%, 91%, 88%, 77%, and 68% in the group without AR, respectively. The differences in graft survival were statistically significant ($P = .000$) (Fig 1). Acute rejection did not influence patient survival ($P = .914$). These survival results did not include grafts and patients who had been lost due to nonimmunologic causes (vascular thrombosis and death), before reaching 6 months' survival.

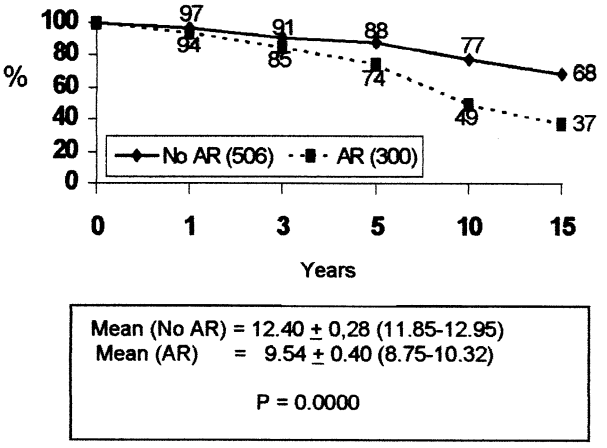

Fig 1. Comparison of graft actuarial survival without AR and with AR (Kaplan-Meier method).

DISCUSSION

The progress of immunosuppression has dramatically changed the incidence and consequences of AR. Therefore, graft loss secondary to AR has become quite uncommon. Despite this progress, the role of AR in the development of CD is incontrovertible,[1] and CD appears to be one of the principal causes of graft failure. Ferguson et al[5] showed that the number of AR episodes was the most relevant factor for long-term cadaver kidney allograft outcome, and Matas[6] emphasized that one AR episode is enough to decrease long-term graft survival. In the present study, AR was responsible for only 4.7% of graft loss, but CD emerged as the second cause of graft failure, with a 30.5% rate. Our results (Table 2) clearly show that AR was the most important factor for CD (12% without AR vs 40% with AR). The AR immunological damage promotes a local cytokine release, inducing progressive nephron damage and renal mass destruction, with development of a fibrotic repair that ends in CD.[2] Hyperfiltration in the remnant nephrons, leading to glomerulosclerosis, also plays a role in the evolution to organ failure.[2,4] Basadonna et al[7] showed a CD occurrence of less than 1% at 5 years without AR and about 50% with previous AR.

Table 2. Influence of Acute Rejection on the Evolution of the Transplant

Factors	*P* Value	Odds Ratio	CI 95%
SCr at 1 year >1.2 mg/dL	.000	2.358	1.742–3.191
Chronic dysfunction	.000	4.819	3.360–6.912

Abbreviations: SCr, serum creatinine.

Concerning the increase in AR among grafts from cadaver donors whose cause of death was cerebrovascular stroke with a prolonged history of arterial hypertension, Guidi et al[8] reported that a grafted kidney from a hypertensive donor could transmit not only chronic hypertension, but also more severe kidney impairment after an acute insult (Table 1). It has been reported that perfusion with Euro-Collins solution and prolonged cold ischemia times are associated with an easier development of ischemia-reperfusion lesions that increase both graft immunogenicity and the rate of AR.[4]

The higher AR rate that we observed in younger recipients (<45 years) probably indicates a stronger innate immune responsiveness in these patients.[3] Confirming this hypothesis, Cecka observed that, in young patients, immunologic graft failures were more frequent.[1] Like others[9] we did not find any statistically significant difference ($P = .292$) between the two groups based upon the number of HLA mismatches (6, 5, 4 vs 3, 2, 1) under CyA-based therapy. The immunosuppressive protocol that showed a higher AR incidence was the association of ALG + Aza + Pred + CyA, a protocol that sought to decrease DGF incidence by avoiding early CyA nephrotoxicity. Therefore, CyA administration was delayed until onset of diuresis. However, when CyA was initiated and ALG was stopped, we noted a high AR incidence (46%), despite 2 days of concomitant therapy. Another finding in our study was the increase of AR among patients with DGF (Table 1) an observation attributed to the increase graft immunogenicity, caused by DGF

wherein the ischemic tubular cells[10] upregulate foreign histocompatibility antigen expression. Furthermore, graft function at 1 year evaluated as a SCr >1.2 mg/dL was significantly worse (46% vs 27%) among patients with AR (Table 2).

We conclude that acute rejection persists as an important and complex factor leading to chronic allograft dysfunction, being the second cause of kidney graft loss following death with a functioning graft. In this study the most relevant factors for AR were recipient age <45 years, immunosuppressive therapy without CyA, delayed graft function, perfusion with Euro-Collins solution, and prolonged cold ischemia times (>24 hours). The worse graft function at 1 year in patients with AR episodes heralds the later development of chronic dysfunction.

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